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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
HIROTOSHI ISHIDA, ET AL.	: EXAMINER: TRAN LIEN, THUY
SERIAL NO: 10/722,679 and 90/007,160	:
FILED: NOVEMBER 28, 2003	: GROUP ART UNIT: 1761
FOR: SWEETENER COMPOSITION	:

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR 1.97

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

Pursuant to 37 C.F.R. §1.56 and 37 C.F.R. §1.97, Applicants wish to make of record the following information:

Applicants undertook testing to confirm if pure C-type crystal of N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester ("DMB-APM" or "neotame") is obtained by the conditions described in U.S. Patent No. 5,480,668, as described at col. 7, lines 24-51, or in U.S. Patent No. 5,728,862, as described at col. 4, lines 32-49.

Preparation of Test Samples

(1) Run 1: A methanol/water solvent according to U. S. Patent 5,728,862 (17-25% aqueous methanol solution) was prepared by mixing 30.05 g of methanol and 105.17 of water. Thereafter, 6.41 g of DMB-APM (NutraSweet Co.'s Neotame lot # D106023325) was added to 49.92 g of the solvent and dissolved completely by heating to 60°C. The amount of DMB-APM was determined according to the preliminary test to study the amounts in which crystals

were obtained when cooled down to 10°C. The cooling crystallization according to U.S. Patent 5,728,862 was carried out at 10-15°C for 2 to 12 hours. The solution was cooled down from 60 to 10°C at a rate of 10°C per hour and then kept at 10°C for crystallization. The precipitated solid was filtered by suction filtration and dried by vacuum drier (Yamato Scientific Co's DP33) at 40°C for 16 hours. Crystalline sample was obtained.

(2) Run 2: An ethanol/water solvent according to U.S. Patent No. 5,480,668 was prepared by mixing 25 ml of ethanol and 25 ml of water. Thereafter, 11.06 g of DMB-APM (NutraSweet Co.'s Neotame lot # D106023325) was added to 30.05 g of the solvent and dissolved completely by heating to 60°C. The amount of DMB-APM was determined according to the preliminary test to study the amounts in which crystals were obtained when cooled down to 10°C. The cooling crystallization was carried out at 10-15°C for 2 to 12 hours, as in U.S. Patent No. 5,728,862. The solution was cooled down from 60 to 10°C at a rate of 10°C per hour and then kept at 10°C for crystallization. The precipitated solid was filtered by suction filtration and dried by vacuum drier (Yamato Scientific Co's DP33) at 40°C for 16 hours. Crystalline sample was obtained.

(3) Run 3: Acetonitrile was used as solvent according to U.S. Patent No. 5,480,668. 17.51 g of DMB-APM (NutraSweet Co.'s Neotame lot # D106023325) was added to 20.1 g of acetonitrile and dissolved completely by heating to 60°C. The amount of DMB-APM was determined according to the preliminary test to study the amounts in which crystals were obtained when cooled down to 10°C. The cooling crystallization was carried out at 10-15°C for 2 to 12 hours, as in U.S. Patent No. 5,728,862. The solution was cooled down from 60 to 10°C at a rate of 10°C per hour and then kept at 10°C for crystallization. The precipitated

solid was filtered by suction filtration and dried by vacuum drier (Yamato Scientific Co's DP33) at 40°C for 16 hours. Crystalline sample was obtained.

(4) Run 4: A methanol/water solvent according to U.S. Patent No. 5,728,862 (17-25% aqueous methanol solution) was prepared by mixing 30.05 g of methanol and 105.17 of water. Thereafter, 4.2 g of DMB-APM (NutraSweet Co.'s Neotame lot # D106023325) was added to 20.24 g of the solvent and dissolved completely by heating to 60°C. The amount of DMB-APM was determined according to the preliminary test to study the amounts in which crystals were obtained when cooled down to 10°C. The cooling crystallization was carried out at 10-15°C for 2 to 12 hours, as in U.S. Patent No. 5,728,862. The solution was cooled down from 60 to 10°C at a rate of 10°C per hour and then kept at 10°C for crystallization. The precipitated solid was filtered by suction filtration and dried by vacuum drier (Yamato Scientific Co's DP33) at 40°C for 16 hours. Crystalline sample was obtained.

(5) Run 5: An ethanol/water solvent according to U.S. Patent No. 5,480,668 was prepared by mixing 25 ml of ethanol and 25 ml of water. Thereafter, 9.84 g of DMB-APM (NutraSweet Co.'s Neotame lot # D106023325) was added to 20.06 g of the solvent and dissolved completely by heating to 60°C. The amount of DMB-APM was determined according to the preliminary test to study the amounts in which crystals were obtained when cooled down to 10°C. The cooling crystallization was carried out at 10-15°C for 2 to 12 hours, as in U.S. Patent No. 5,728,862. The solution was cooled down from 60 to 10°C at a rate of 10°C per hour and then kept at 10°C for crystallization. The precipitated solid was filtered by suction filtration and dried by vacuum drier (Yamato Scientific Co's DP33) at 40°C for 16 hours. Crystalline sample was obtained.

(6) Run 6: Acetonitrile was used as solvent according to U.S. Patent 5,480,668. 10.47 g of DMB-APM (NutraSweet Co.'s Neotame lot # D106023325) was added to 20.18 g of acetonitrile and dissolved completely by heating to 60°C. The amount of DMB-APM was determined according to the preliminary test to study the amounts in which crystals were obtained when cooled down to 10°C. The cooling crystallization was carried out at 10-15°C for 2 to 12 hours, as in U.S. Patent No. 5,728,862. The solution was cooled down from 60 to 10°C at a rate of 10°C per hour and then kept at 10°C for crystallization. The precipitated solid was filtered by suction filtration and dried by vacuum drier (Yamato Scientific Co's DP33) at 40°C for 16 hours. Crystalline sample was obtained.

Analyses

Water content of the dried sample was analyzed by Karl-Fischer moisture analyzer MKA-210 (Kyoto Electronics Manufacturing Co. Ltd) and crystal type was analyzed by X ray diffractometer (PANalytical's X'Pert with X'Celerator, Tube:Cu,30mA,40kV,Sampling width: 0.020°,scanning speed :3°/min, wave length:1.54056Å, 2θ:4-30°).

Result

The results are shown in Table 1.

Table 1.

	Solvent USPatent		Amount of added neotame	Concentration of added neotame	Temp. of precipitation	Time of precipitation	Amount of crystal	Water content	Type of crystal
			(g)	(weight %)	(℃)	(hr:min)	(g)	(weight %)	
Added neotame	-	-	-	-	-	-	-	5.812	A
Run-1	MeOH:H_2O	5,728,862	6.41	11.38	18.90	4:12	4.72	0.4083	G
Run-2	EtOH:H_2O	5,480,668	11.06	26.90	12.44	4:50	6.80	0.184	G
Run-3	MeCN	5,480,668	17.51	46.56	16.78	4:25	16.51	0.1223	A+C
Run-4	MeOH:H_2O	5,728,862	4.20	17.18	10.10	5:36	4.21	10.144	A+F
Run-5	EtOH:H_2O	5,480,668	9.84	32.91	10.87	4:58	8.69	3.3418	G
Run-6	MeCN	5,480,668	10.47	34.16	10.00	8:25	3.25	0.2451	A+C

Applicants respectfully request due consideration of this information.

Respectfully submitted,

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